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REVIEW

Diabetes Mellitus Is Associated with Occult Cancer in Endometrial Hyperplasia

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Abstract

In the management of women diagnosed with endometrial hyperplasia (EH), it is crucial to determine the risk of coexistent cancer. Diabetes mellitus has been recently suggested as a significant risk factor. However, results in this regard are conflicting. Our aim was to assess the association between diabetes mellitus and coexistent cancer in women diagnosed with endometrial hyperplasia. A systematic review and meta-analysis was performed by searching electronic databases from their inception to October 2018 for studies assessing the presence of coexistent cancer after a preoperative diagnosis of endometrial hyperplasia in women stratified for diabetes mellitus. Odds ratio was calculated with 95% confidence interval; a p value <0.05 was considered significant. Twelve retrospective studies with 1579 EH were included. Diabetes mellitus showed significant association with the presence of cancer coexistent with endometrial hyperplasia (OR = 1.96; 95% CI, 1.07–3.60; $p = 0.03$). Heterogeneity among studies was moderate ($I^2 = 55\%$). Funnel plot showed asymmetric distribution of OR values, with the large and accurate studies showing results stronger than small and less accurate one; this finding should exclude a publication bias. In women diagnosed with endometrial hyperplasia, diabetes mellitus is a risk factor for coexistent cancer, and thus may be included in a predictive algorithm for the risk stratification. In women conservatively treated, glycemic control may be required to prevent the risk of progression. Further studies are necessary to confirm the clinical significance of diabetes mellitus in this field.

Keywords Concurrent cancer · Endometrial cancer · Endometrial intraepithelial neoplasia · Glycemia · Occult cancer · Risk

Introduction

Endometrial hyperplasia (EH) is an irregular proliferation of endometrial glands with a gland to stroma ratio higher than the normal endometrium in the proliferative phase [1].

EH can precede or coexist with endometrial cancer (EC), endometrioid type ("type I" EC in the Bokhman classification) [1, 2]. Histological studies of EH have focused on the definition of the characteristics that correlate with higher risk of EC [2]. The main morphologic factors associated with the risk of cancer are cytologic atypia, glandular crowding and appearance different from adjacent endometrium [2–4]. However, histomorphologic features have shown low reproducibility among pathologists [5], and several problems may affect the diagnosis on biopsy specimens, such as tissue inadequacy or artifact changes [6].

Molecular features of EH may also be useful to recognize precancerous lesions; in particular, aberrant expression of markers involved in endometrial carcinogenesis may be studied by immunohistochemistry in EH specimens [2, 7–10].

Given that also clinical data may impact on the risk of EC, several authors tried to elaborate an algorithm to predict of cancer in EH [11–13]. Nonetheless, a reliable predictive model has never been achieved, in particular because data in this field are conflicting, and the actual relevance of certain parameters is undefined.

In recent years, diabetes mellitus has been proposed as a factor independently associated with the risk of coexistent EC in patients diagnosed with EH on endometrial biopsy [13].

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Objective of our study was to assess if diabetes mellitus is a risk factor for coexistent cancer in EH. We aimed to define whether or not diabetes mellitus should be considered in the preoperative assessment of EH.

Materials and Methods

Methods for collection, extraction and analysis of data, and for risk of bias assessment, were defined a priori. Three authors (AR, AT, GS) independently performed all review stages, and disagreements were resolved by discussion with a fourth author (MM).

This study was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [14].

Search Strategy

MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, Cochrane Library, OVID, and Google Scholar were searched for relevant articles from the inception of each database to October 2018. Several different combinations of the following text words were used: "endometrial hyperplasia"; "endometrial intraepithelial neoplasia"; "EIN"; "diabetes"; "cancer"; "carcinoma"; "adenocarcinoma"; "endometrioid"; "precancer"; "premalignant"; "precursor"; "coexistent"; "concurrent"; "occult"; "biopsy"; "sampling"; "preoperative"; "hysterectomy". All relevant references were also reviewed.

Study Selection

We included all peer-reviewed retrospective or prospective studies meeting the following inclusion criteria:

- sample constituted by women diagnosed with EH and who underwent hysterectomy;
- assessment of the presence of EC on histologic examination of hysterectomy specimen;
- assessment of the association between diabetes mellitus and presence of EC on hysterectomy.

Exclusion criteria, defined a priori, were:

- data not extractable;
- case reports and reviews;
- overlapping patient data with a study already included.

Assessment of Risk of Bias among Studies

The Methodological Index for NOn-Randomized Studies (MINORS) was used to assess the risk of bias among the included studies [15]. Five domains related to the risk of bias were considered applicable to the included studies: 1) Aim (i.e. clearly stated aim); 2) Inclusion of consecutive patients (i.e. inclusion of all eligible patients in the period of study); 3) Endpoints appropriate to the aim (i.e. unambiguous explanation of the criteria used to measure outcomes); 4) Unbiased assessment of endpoints (i.e. unbiased assessment of the study endpoints); 5) Follow-up period appropriate to the aim (i.e. if the time interval between index biopsy and hysterectomy was <1 year; in fact, only EC diagnosed within 1 year from EH diagnosis are accepted as "coexistent" cancers in the literature [16, 17]).

Review authors' judgments were categorized as "low risk of bias", "high risk of bias" or "unclear risk" of bias if data about the domain were "reported and adequate", "reported but inadequate" and "not reported", respectively.

Data Extraction and Analysis

Data were extracted from eligible studies without modification. Two by two contingency tables were prepared for each study, reporting two dichotomous qualitative variables: presence of diabetes mellitus and presence of cancer on the subsequent hysterectomy.

Diabetes mellitus was defined as hemoglobin A1c level of 6.5% or greater, a fasting plasma glucose level of 126 mg/dL or greater, or a 2-h plasma glucose level of 200 mg/dL or greater [18].

Odds ratio (OR) was calculated for each study and as pooled estimate with 95% confidence interval (CI). Statistical heterogeneity among studies was quantified by using the inconsistency index (I^2): heterogeneity was considered insignificant for $I^2 < 25\%$, low for $I^2 < 50\%$, moderate for $I^2 < 75\%$ and high for $I^2 \geq 75\%$. In case of $I^2 < 50\%$, the fixed effect model of Mantel-Haenszel was used; otherwise, a random effect model was used. Results were reported graphically on a forest plot.

The risk of bias across studies (publication bias) was assessed by reporting OR on x axis and standard error on y axis on a funnel plot; asymmetry of funnel plot suggests publication bias if little accurate studies (high standard error) have stronger results (higher OR) than more accurate ones.

The data analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014).

Results

Selection and Characteristics of the Studies

Twelve retrospective studies, assessing a total sample of 1579 women diagnosed with EH, were included [11–13, 19–27]. Details about the whole process of study selection are shown in Fig. 1.

Sampling methods included curettage, pipelle biopsy, hysteroscopic biopsy and hysteroscopic resection.

Details about characteristics of the included studies are shown in Table 1.

Assessment of Risk of Bias among Studies

For the "Aim", "Endpoints appropriate to the aim" and "Unbiased assessment of endpoints" domains, no particular sources of bias were found. Therefore, all studies were considered at low risk of bias.

For the "Inclusion of consecutive patients" domain, 3 studies were considered at low risk of bias, since they clearly stated that patients were selected consecutively; the other 11 studies reported inclusion criteria and period of enrollment, but it was unclear whether all patients were selected, hence the unclear risk of bias.

For the "Follow-up period appropriate to the aim" domain, 5 studies were considered at low risk, since they specified that all patients underwent hysterectomy within 1 year from the index diagnosis. Six studies only stated that all biopsies were in the preoperative phase, or reported the mean/median interval, and thus they were considered at unclear risk. One study was considered at high risk, because some patients had an index biopsy-to-hysterectomy interval > 1 year.

Results of risk of bias assessment are shown in Fig. 2.

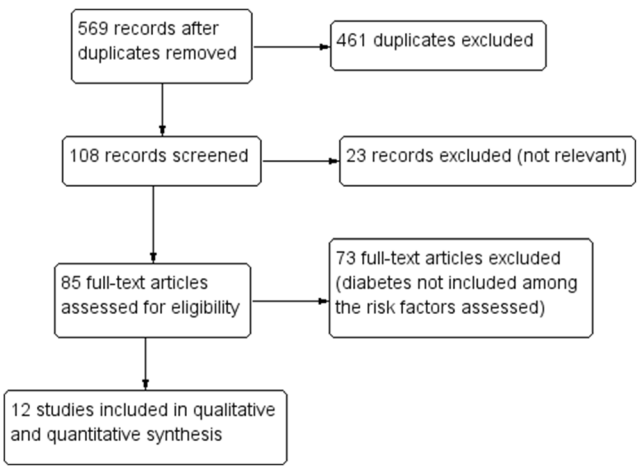

Fig. 1 Flow diagram of studies identified in the systematic review (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses])

Meta-Analysis

Diabetes mellitus showed significant association with the presence of cancer coexistent with EH (OR = 1.96; 95% CI, 1.07–3.60; $p = 0.03$). There was moderate heterogeneity among studies ($I^2 = 55\%$) (Fig. 3).

Funnel plot showed asymmetric distribution of OR values, with the large and accurate studies showing results stronger than small and less accurate one; this finding should exclude the possibility of a publication bias (Fig. 4).

Discussion

Our study showed that, in women diagnosed with EH, diabetes mellitus was significantly associated with the risk of coexistent cancer. To the best of our knowledge, this is the first systematic review and meta-analysis assessing the association between diabetes mellitus and coexistent EC in EH.

The stratification of the risk of EC in EH is a long-standing issue. Several histologic classifications had been proposed, such as "mild", "moderate" and "severe", or "cystic glandular", "adenomatous" and "adenomatous atypical", or "simple", "complex" and atypical" [2, 28–30]. The 2014 WHO classification indicates cytologic atypia as the crucial feature for differentiating precancerous EH from benign EH [1]. On the other hand, the endometrial intraepithelial neoplasia (EIN) classification proposes a combination of 3 morphological features (glandular crowing, lesion size >1 mm, cytology different from adjacent endometrium) [3, 4, 30]. None of these features perfectly reflects the risk of cancer, but they may show different values of sensitivity and specificity [3]. Based on this finding, a novel integration of both classification systems has been recently proposed in order to better stratify the risk of coexistent EC. Such novel classification separates EH into three histologic categories: benign EH, EIN without cytologic atypia (at lower risk) and EIN with cytologic atypia (at higher risk) [3, 29]. Unfortunately, the inter- and intra-observer reproducibility of histologic examination is suboptimal [5].

Several molecular and immunohistochemical markers have been also studied to identify precancerous EH, but none appeared reliable as a stand-alone marker [2, 7–9]. In particular, PTEN, the key molecule in endometrial carcinogenesis, has shown low diagnostic accuracy in the differential diagnosis between benign and precancerous EH [9, 31].

Table 1 Characteristics of the included studies

Study	Country	Period of enrollment	Sample size	Mean age	Mean BMI	Mean gravidity	Mean parity	Sampling method	Time to hysterectomy
1995 Widra [19]	USA	1988–1993	45	54.4	n.r. (26 obese)	2.7	2.2	hysteroscopy, curettage, biopsy (unspecified)	preoperative (mean 2.4 months)
2005 Bilgin [20]	Turkey	5 year	46	49.1	n.r.	3.9	3.2	pipelle, curettage	< 6 weeks
2005 Merisio [21]	Italy	1992–2003	70	55.5	n.r. (16 obese)	n.r.	1.7	curettage, pipelle	2–8 weeks
2009 Chen [11]	Taiwan	1996–2006	77	49.6	25.6	3.4	2.5	curettage	preoperative (unspecified)
2011 Daud [22]	UK	1998–2009	280	55.7	n.r. (105 obese)	n.r.	2.0	pipelle, curettage	2 weeks to 3 years (median 2 months)
2012 Robbe [23]	Belgium Netherlands	1999–2006	39	60.4	31.9	n.r.	2.4	pipelle, curettage	2–37 weeks (median 6 weeks)
2013 Chen [12]	Taiwan	1991–2009	381	49.7	n.r. (117 obese)	n.r. (52 nulligravid)	n.r. (56 nulliparous)	curettage, pipelle, hysteroscopy	preoperative (unspecified)
2014 Touboul [24]	France	2002–2012	78	60.1	30.3	n.r.	n.r.	hysteroscopy, curettage, resection	median 64 days
2014 Zhou [25]	China	2008–2013	149	53.6	n.r.	n.r.	1.3	curettage, hysteroscopy	< 6 months
2015 Dolanbay [26]	Turkey	2009–2013	82	54.6	29.3	n.r.	2.7	pipelle, biopsy (unspecified)	< 6 weeks
2015 Kadirogullari [27]	Turkey	2006–2012	139	50.5	30.4	n.r.	3.0	biopsy (unspecified)	preoperative (unspecified)
2015 Matsuo [13]	USA	2003–2014	211	45.2	35.6	2.0	n.r.	pipelle, vacuum aspiration, curettage	median 105 days
Total	–	1988–2014	1597	–	–	–	–	–	–

n.r. not reported

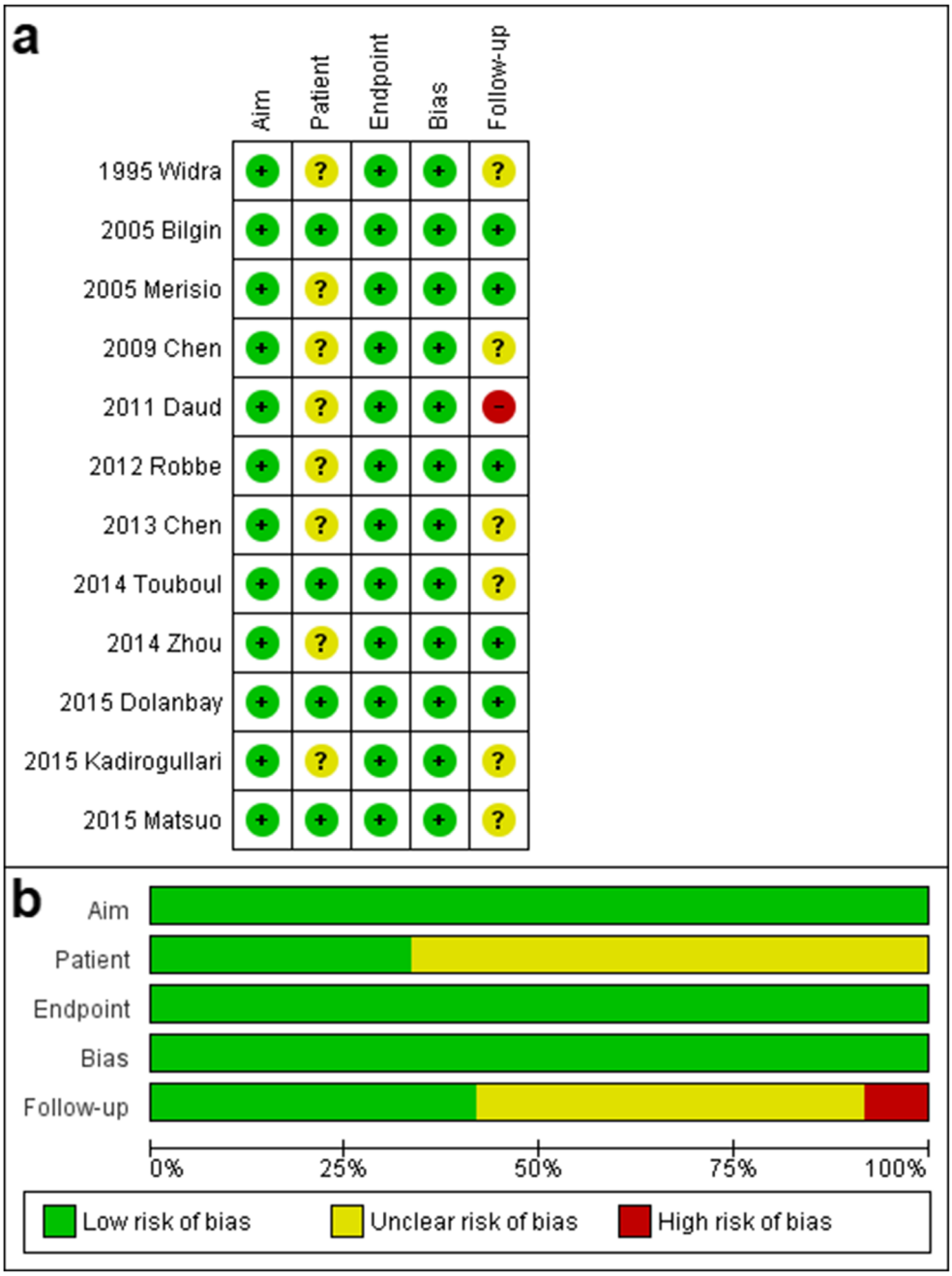

Fig. 2 **a** Assessment of risk of bias. Summary of risk of bias for each study; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. **b** Risk of bias graph about each risk of bias item presented as percentages across all included studies

Regarding clinical factors, some factors involved in the absolute risk of EC, such as BMI, age and parity, might have a prognostic significance for the risk of coexistent EC in EH [11–13, 19–27].

In our study, we focused on diabetes mellitus. The relationship between diabetes mellitus and EC is controversial. In fact, some authors advocate the importance of diabetes mellitus as a risk factor for EC, while other ones suggest that such association was not independent, but it was affected by BMI, as obesity correlates to insulin-resistance [32, 33]. A recent umbrella review concluded that, unlike BMI, further evidence is necessary regarding the association between diabetes mellitus and EC [32].

In the 2015, Matsuo et al. performed a case-control study, searching for factors associated with the risk of coexistent cancer in 211 women preoperatively diagnosed with EH. They found that the presence of complex atypical EH, older age, obesity and diabetes mellitus were risk factors for coexistent EC. The significance of diabetes mellitus was subsequently confirmed at the multivariate

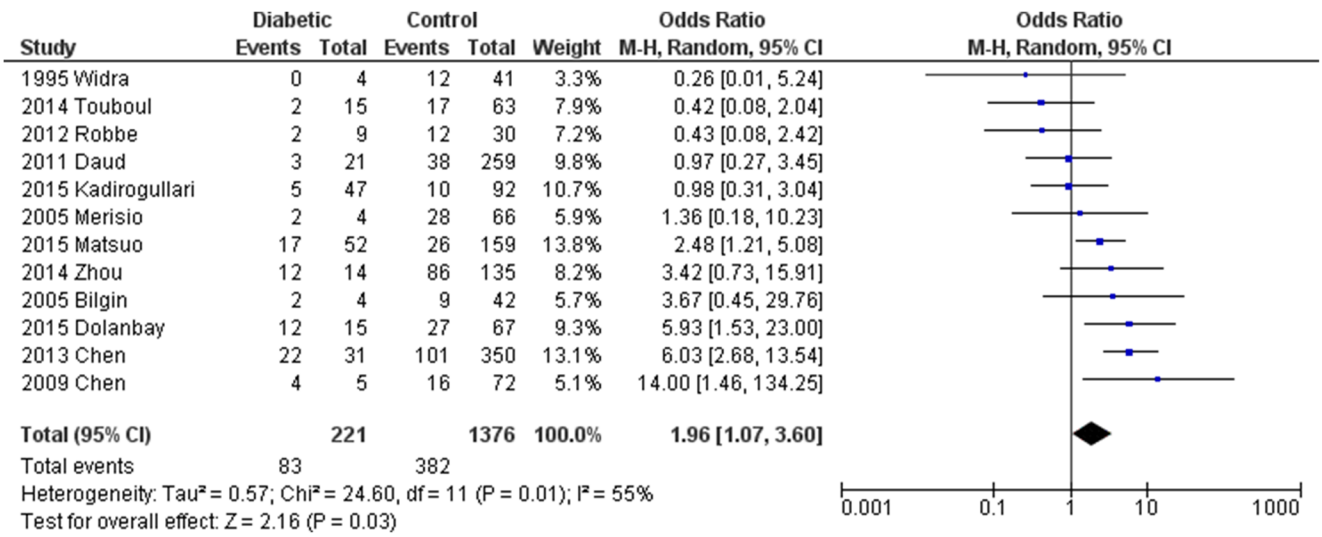

Fig. 3 Forest plot reporting odds ratio (OR) of individual studies and as pooled estimate, with 95% confidence interval (CI), for the risk of coexistent cancer in diabetic women with endometrial hyperplasia vs non-diabetic ones

analysis, demonstrating its independence from obesity [13].

In our current study, we found that diabetes mellitus was significantly associated with the risk of EC coexistent with EH.

Diabetes mellitus, in particular type II, is characterized by a hyperinsulinic state, which leads to an increase in the available circulating levels of insulin like growth factor 1 (IGF-1), favoring the activation of pro-proliferative kinase pathways [34]. The activation of these pathways might promote the progression form EH to EC.

Our findings are consistent with the results from a recent meta-analysis, which showed that diabetes mellitus was associated with the risk of EC coexistent with endometrial polyps [35].

Diabetes mellitus may be a major non-histologic and non-molecular factor which affects the risk of progression of EH to

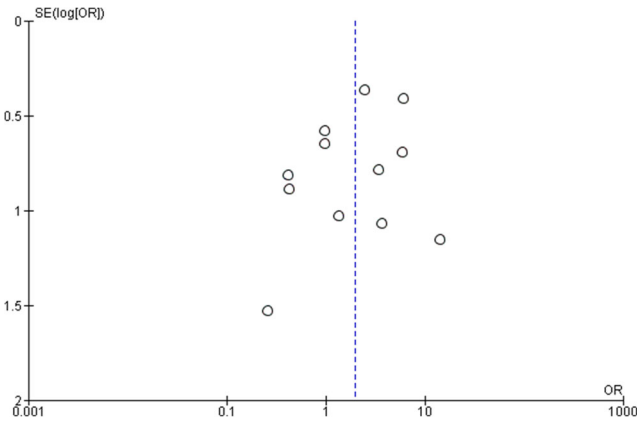

Fig. 4 Funnel plot for the assessment of the risk of bias across studies (publication bias). Odds ratio (OR) values are reported on the *x* axis and standard error (SE) values on the *y* axis

EC. To date, management of patients with EH is mainly based on histological features of EH, and cytologic atypia is the most important parameter. In fact, while non-atypical EH may be managed by observation alone, atypical EH requires total hysterectomy, with conservative approaches (e.g. oral progestins, medicated intrauterine device, hysteroscopic resection) reserved to selected cases [36–39]. Diabetes mellitus may be integrated in a predictive algorithm for the risk of coexistent EC, together with other clinical, histomorphologic and immunohistochemical parameters, in order to achieve a more tailored management of the patients. Women with EH at higher risk for EC may have a higher surgical priority if hysterectomy is chosen, or they may require a closer and more careful follow-up in case of conservative treatment (every 3 months rather than 3–6 months, as actually recommended [36]). Furthermore, in women conservatively treated, an adequate glycemic control may be necessary to reduce the risk of progression to cancer. In this regard, it has been proposed that metformin, a major anti-diabetic drug, may be useful in the conservative treatment of EH [40]. It would be interesting to assess how diabetes mellitus may affect the outcome of the conservative treatment of EH, as molecular markers appear inadequate to predict the outcome [41–43]. However, in our previous study we found that diabetes mellitus did not seem to significantly affect the responsiveness of EH to progestins [44].

A limitation to our results may lie in the retrospective design of the included studies; such a limitation may be tempered by the inclusion of consecutive patients.

Our results might be affected by a significant heterogeneity among studies. However, according to the funnel plot, small and heterogeneous studies showed lower OR values compared to the larger and more homogeneous studies. This

finding indicates not only that publication bias is not present, but also that the actual association between diabetes mellitus and risk of coexistent cancer may be higher.

Further studies are necessary to confirm the prognostic relevance of diabetes mellitus in women diagnosed with EH and its usefulness in the patient management.

Conclusion

Diabetes mellitus in women diagnosed with EH appears as a risk factor for coexistent EC. Diabetes mellitus might be included in a predictive algorithm for the risk of EC in EH, together with other clinical, histologic and immunohistochemical data, in order to tailor the management of patients with EH. An adequate glycemic control might be required in women with EH in order to reduce the risk of imminent progression.

Further studies are necessary to confirm the clinical applicability of diabetes mellitus in the risk stratification of EH.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Not applicable.

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